



SEQUENCE LISTING

<110> Roy A. Gravel et al.

<120> HUMAN METHIONINE SYNTHASE REDUCTASE:  
CLONING, AND METHODS FOR EVALUATING RISK OF NEURAL TUBE  
DEFECTS, CARDIOVASCULAR DISEASE, AND CANCER

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<140> 09/371,347

<141> 1999-08-10

<150> 60/071,622

<151> 1998-01-16

<150> 09/232,028

<151> 1999-01-15

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<170> FastSEQ for Windows Version 4.0

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cctgcgggat	gttctctcca	gttcattttt	acctgggtgc	ttgaaatccg	agcaattcct	1140
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<212> PRT

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Ala	Asp	Leu	His	Cys	Ile	Ser	Glu	Ser	Asp	Lys	Tyr	Asp	Leu	Lys	Thr
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Glu	Thr	Ala	Pro	Leu	Val	Val	Val	Ser	Thr	Thr	Gly	Thr	Gly	Asp	
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Leu	Pro	Val	Asp	Phe	Phe	Ala	His	Leu	Arg	Tyr	Gly	Leu	Leu	Gly	Leu
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Ala	Asp	Asp	Cys	Val	Gly	Leu	Glu	Leu	Val	Val	Glu	Pro	Trp	Ile	Ala
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Gly	Leu	Trp	Pro	Ala	Leu	Arg	Lys	His	Phe	Arg	Ser	Ser	Arg	Gly	Gln
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Glu	Glu	Ile	Ser	Gly	Ala	Leu	Pro	Val	Ala	Ser	Pro	Ala	Ser	Leu	Arg
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Thr	Asp	Leu	Val	Lys	Ser	Glu	Leu	Leu	His	Ile	Glu	Ser	Gln	Val	Glu
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Leu	Leu	Arg	Phe	Asp	Asp	Ser	Gly	Arg	Lys	Asp	Ser	Glu	Val	Leu	Lys
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Gln	Asn	Ala	Val	Asn	Ser	Asn	Gln	Ser	Asn	Val	Val	Ile	Glu	Asp	Phe
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Ser Leu Gly Gln Glu	Glu Ser Gln Val Ser	Val Thr Ser Ala Asp	Pro			
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Val Phe Gln Val Pro	Ile Ser Lys Ala Val	Gln Leu Thr Thr	Asn Asp			
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Ala Ile Lys Thr Thr	Leu Leu Val Glu Leu	Asp Ile Ser Asn Thr	Asp			
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Phe Ser Tyr Gln Pro	Gly Asp Ala Phe Ser	Val Ile Cys Pro Asn	Ser			
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Asp Ser Glu Val Gln	Ser Leu Leu Gln Arg	Leu Gln Leu Glu Asp	Lys			
	325		330		335	
Arg Glu His Cys Val	Leu Leu Lys Ile Lys	Ala Asp Thr Lys Lys	Lys			
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Gly Ala Thr Leu Pro	Gln His Ile Pro Ala	Gly Cys Ser Leu Gln	Phe			
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Ile Phe Thr Trp Cys	Leu Glu Ile Arg Ala	Ile Pro Lys Lys Ala	Phe			
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Leu Arg Ala Leu Val	Asp Tyr Thr Ser Asp	Ser Ala Glu Lys Arg	Arg			
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Leu Gln Glu Leu Cys	Ser Lys Gln Gly Ala	Ala Asp Tyr Ser Arg	Phe			
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Val Arg Asp Ala Cys	Ala Cys Leu Leu Asp	Leu Leu Leu Ala Phe	Pro			
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Ser Cys Gln Pro Pro	Leu Ser Leu Leu Leu	Glu His Leu Pro Lys	Leu			
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Gln Pro Arg Pro Tyr	Ser Cys Ala Ser Ser	Ser Leu Phe His Pro	Gly			
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Lys Leu His Phe Val	Phe Asn Ile Val Glu	Phe Leu Ser Thr Ala	Thr			
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Thr Glu Val Leu Arg	Lys Gly Val Cys Thr	Gly Trp Leu Ala Leu	Leu			
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Val Ala Ser Val Leu	Gln Pro Asn Ile His	Ala Ser His Glu Asp	Ser			
	500		505		510	
Gly Lys Ala Leu Ala	Pro Lys Ile Ser Ile	Ser Pro Arg Thr Thr	Asn			
	515		520		525	
Ser Phe His Leu Pro	Asp Asp Pro Ser Ile	Pro Ile Ile Met Val	Gly			
	530		535		540	
Pro Gly Thr Gly Ile	Ala Pro Phe Ile Gly	Phe Leu Gln His Arg	Glu			
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Lys Leu Gln Glu Gln	His Pro Asp Gly Asn	Phe Gly Ala Met Trp	Leu			
	565		570		575	
Phe Phe Gly Cys Arg	His Lys Asp Arg Asp	Tyr Leu Phe Arg Lys	Glu			
	580		585		590	
Leu Arg His Phe Leu	Lys His Gly Ile Leu	Thr His Leu Lys Val	Ser			
	595		600		605	
Phe Ser Arg Asp Ala	Pro Val Gly Glu Glu	Glu Ala Pro Ala Lys	Tyr			
	610		615		620	
Val Gln Asp Asn Ile	Gln Leu His Gly Gln	Gln Val Ala Arg Ile	Leu			
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Leu Gln Glu Asn Gly His Ile Tyr Val Cys Gly Asp Ala Lys Asn Met  
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 Ala Lys Asp Val His Asp Ala Leu Val Gln Ile Ile Ser Lys Glu Val  
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 Gly Val Glu Lys Leu Glu Ala Met Lys Thr Leu Ala Thr Leu Lys Glu  
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 Pro Pro Asp Thr Ala Arg Lys Phe Val Lys Glu Ile Gln Asn Gln Thr  
 65 70 75 80  
 Leu Pro Val Asp Phe Phe Ala His Leu Arg Tyr Gly Leu Leu Gly Leu  
 85 90 95  
 Gly Asp Ser Glu Tyr Thr Tyr Phe Cys Asn Gly Gly Lys Ile Ile Asp  
 100 105 110  
 Lys Arg Leu Gln Glu Leu Gly Ala Arg His Phe Tyr Asp Thr Gly His  
 115 120 125  
 Ala Asp Asp Cys Val Gly Leu Glu Leu Val Val Glu Pro Trp Ile Ala  
 130 135 140  
 Gly Leu Trp Pro Ala Leu Arg Lys His Phe Arg Ser Ser Arg Gly Gln  
 145 150 155 160  
 Glu Glu Ile Ser Gly Ala Leu Pro Val Ala Ser Pro Ala Ser Leu Arg  
 165 170 175  
 Thr Asp Leu Val Lys Ser Glu Leu Leu His Ile Glu Ser Gln Val Glu  
 180 185 190  
 Leu Leu Arg Phe Asp Asp Ser Gly Arg Lys Asp Ser Glu Val Leu Lys  
 195 200 205  
 Gln Asn Ala Val Asn Ser Asn Gln Ser Asn Val Val Ile Glu Asp Phe  
 210 215 220  
 Glu Ser Ser Leu Thr Arg Ser Val Pro Pro Leu Ser Gln Ala Ser Leu  
 225 230 235 240  
 Asn Ile Pro Gly Leu Pro Pro Glu Tyr Leu Gln Val His Leu Gln Glu  
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 Ser Leu Gly Gln Glu Glu Ser Gln Val Ser Val Thr Ser Ala Asp Pro  
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 275 280 285  
 Ala Ile Lys Thr Thr Leu Leu Val Glu Leu Asp Ile Ser Asn Thr Asp  
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 Phe Ser Tyr Gln Pro Gly Asp Ala Phe Ser Val Ile Cys Pro Asn Ser  
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 Asp Ser Glu Val Gln Ser Leu Leu Gln Arg Leu Gln Leu Glu Asp Lys  
 325 330 335  
 Arg Glu His Cys Val Leu Leu Lys Ile Lys Ala Asp Thr Lys Lys Lys  
 340 345 350  
 Gly Ala Thr Leu Pro Gln His Ile Pro Ala Gly Cys Ser Leu Gln Phe

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Ile Phe Thr Trp Cys Leu Glu	Ile Arg Ala Ile Pro Lys Lys Ala Phe			
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Leu Gln Glu Leu Cys Ser Lys Gln Gly Ala Ala Asp Tyr Ser Arg Phe				
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Val Arg Asp Ala Cys Ala Cys Leu Leu Asp Leu Leu Leu Ala Phe Pro				
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Ser Cys Gln Pro Pro Leu Ser Leu Leu Leu Glu His Leu Pro Lys Leu				
435	440	445		
Gln Pro Arg Pro Tyr Ser Cys Ala Ser Ser Ser Leu Phe His Pro Gly				
450	455	460		
Lys Leu His Phe Val Phe Asn Ile Val Glu Phe Leu Ser Thr Ala Thr				
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Thr Glu Val Leu Arg Lys Gly Val Cys Thr Gly Trp Leu Ala Leu Leu				
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Val Ala Ser Val Leu Gln Pro Asn Ile His Ala Ser His Glu Asp Ser				
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Gly Lys Ala Leu Ala Pro Lys Ile Ser Ile Ser Pro Arg Thr Thr Asn				
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Ser Phe His Leu Pro Asp Asp Pro Ser Ile Pro Ile Ile Met Val Gly				
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Pro Gly Thr Gly Ile Ala Pro Phe Ile Gly Phe Leu Gln His Arg Glu				
545	550	555		560
Lys Leu Gln Glu Gln His Pro Asp Gly Asn Phe Gly Ala Met Trp Leu				
565	570	575		
Phe Phe Gly Cys Arg His Lys Asp Arg Asp Tyr Leu Phe Arg Lys Glu				
580	585	590		
Leu Arg His Phe Leu Lys His Gly Ile Leu Thr His Leu Lys Val Ser				
595	600	605		
Phe Ser Arg Asp Ala Pro Val Gly Glu Glu Glu Ala Pro Ala Lys Tyr				
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Val Gln Asp Asn Ile Gln Leu His Gly Gln Gln Val Ala Arg Ile Leu				
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Leu Gln Glu Asn Gly His Ile Tyr Val Cys Gly Asp Ala Lys Asn Met				
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Ala Lys Asp Val His Asp Ala Leu Val Gln Ile Ile Ser Lys Glu Val				
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Glu Lys Arg Tyr Leu Gln Asp Ile Trp Ser				
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Ala Pro Asp Asn Cys Ala Arg Phe Val Arg Arg Ile Asn Arg Asn Ser			
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Leu Glu Asn Glu Tyr Leu Lys Asn Leu Asp Tyr Val Leu Leu Gly Leu			
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Gly Asp Ser Asn Tyr Ser Ser Tyr Gln Thr Ile Pro Arg Lys Ile Asp			
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Ala Asp Asp Gln Val Gly Leu Glu Leu Glu Val Glu Pro Trp Ile Glu			
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Lys Phe Phe Ala Thr Leu Ala Ser Arg Phe Asp Ile Ser Ala Asp Lys			
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Met Asn Ala Ile Thr Glu Ser Ser Asn Leu Lys Leu Asn Gln Val Lys			
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Pro Phe Ile Val Ser Ser Val Ser Asn Arg Lys Leu Pro Glu Asp Thr			
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Lys Leu Glu Trp Gln Asn Leu Cys Lys Met Pro Gly Val Val Thr Lys			
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Pro Phe Glu Val Leu Val Val Ser Ala Glu Phe Val Thr Asp Pro Phe			
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Val Pro Asn Pro Ala Leu Glu Val Asn Phe Ile Leu Lys Arg Cys Gly			
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Val Leu Asp Ile Ala Asp Gln Gln Cys Glu Leu Ser Ile Asn Pro Lys			
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Thr Glu Lys Ile Asn Ala Gln Ile Pro Gly His Val His Lys Ile Thr			
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Gly Arg Pro Leu Ile Arg Val Leu Ala Glu Ser Thr Ser Asp Pro Asn			
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Glu Lys Arg Arg Leu Leu Glu Leu Cys Ser Ala Gln Gly Met Lys Asp			
405	410	415	

Phe Thr Asp Phe Val Arg Thr Pro Gly Leu Ser Leu Ala Asp Met Leu  
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Phe Ala Phe Pro Asn Val Lys Pro Pro Val Asp Arg Leu Ile Glu Leu  
435 440 445  
Leu Pro Arg Leu Ile Pro Arg Pro Tyr Ser Met Ser Ser Tyr Glu Asn  
450 455 460  
Arg Lys Ala Arg Leu Ile Tyr Ser Glu Met Glu Phe Pro Ala Thr Asp  
465 470 475 480  
Gly Arg Arg His Ser Arg Lys Gly Leu Ala Thr Asp Trp Leu Asn Ser  
485 490 495  
Leu Arg Ile Gly Asp Lys Val Gln Val Leu Gly Lys Glu Pro Ala Arg  
500 505 510  
Phe Arg Leu Pro Pro Leu Gly Met Thr Lys Asn Ser Ala Gly Lys Leu  
515 520 525  
Pro Leu Leu Met Val Gly Pro Gly Thr Gly Val Ser Val Phe Leu Ser  
530 535 540  
Phe Leu His Phe Leu Arg Lys Leu Lys Gln Asp Ser Pro Ser Asp Phe  
545 550 555 560  
Val Asp Val Pro Arg Val Leu Phe Phe Gly Cys Arg Asp Ser Ser Val  
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Asp Ala Ile Tyr Met Ser Glu Leu Glu Met Phe Val Ser Glu Gly Ile  
580 585 590  
Leu Thr Asp Leu Ile Ile Cys Glu Ser Glu Gln Lys Gly Glu Arg Val  
595 600 605  
Gln Asp Gly Leu Arg Lys Tyr Leu Asp Lys Val Leu Pro Phe Leu Thr  
610 615 620  
Ala Ser Thr Glu Ser Lys Ile Phe Ile Cys Gly Asp Ala Lys Gly Met  
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35 40 45  
Glu Glu Val Pro Glu Phe Thr Lys Ile Gln Thr Leu Thr Ser Ser Val  
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Arg Glu Ser Ser Phe Val Glu Lys Met Lys Lys Thr Gly Arg Asn Ile  
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Arg	Leu	Ser	Lys	Asp	Ala	His	Arg	Tyr	Gly	Met	Arg	Gly	Met	Ser	Ala	
			100					105					110			
Asp	Pro	Glu	Glu	Tyr	Asp	Leu	Ala	Asp	Leu	Ser	Ser	Leu	Pro	Glu	Ile	
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Asp	Asn	Ala	Leu	Val	Val	Phe	Cys	Met	Ala	Thr	Tyr	Gly	Glu	Gly	Asp	
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Thr	Tyr	Glu	His	Phe	Asn	Ala	Met	Gly	Lys	Tyr	Val	Asp	Lys	Arg	Leu	
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Glu	Gln	Leu	Gly	Ala	Gln	Arg	Ile	Phe	Glu	Leu	Gly	Leu	Gly	Asp	Asp	
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Asp	Gly	Asn	Leu	Glu	Glu	Asp	Phe	Ile	Thr	Trp	Arg	Glu	Gln	Phe	Trp	
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Pro	Ala	Val	Cys	Glu	His	Phe	Gly	Val	Glu	Ala	Thr	Gly	Glu	Glu	Ser	
225					230					235					240	
Ser	Ile	Arg	Gln	Tyr	Glu	Leu	Val	Val	His	Thr	Asp	Ile	Asp	Ala	Ala	
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<212> DNA

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Thr	Asp	Leu	Val	Lys	Ser	Glu	Leu	Leu	His	Ile	Glu	Ser	Gln	Val	Glu				
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Gln	Asn	Ala	Val	Asn	Ser	Asn	Gln	Ser	Asn	Val	Val	Ile	Glu	Asp	Phe				
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Asn	Ile	Pro	Gly	Leu	Pro	Pro	Glu	Tyr	Leu	Gln	Val	His	Leu	Gln	Glu				
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Arg	Glu	His	Cys	Val	Leu	Leu	Lys	Ile	Lys	Ala	Asp	Thr	Lys	Lys	Lys				
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Pro	Gly	Thr	Gly	Ile	Ala	Pro	Phe	Ile	Gly	Phe	Leu	Gln	His	Arg	Glu
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Lys	Leu	Gln	Glu	Gln	His	Pro	Asp	Gly	Asn	Phe	Gly	Ala	Met	Trp	Leu
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Leu	Arg	His	Phe	Leu	Lys	His	Gly	Ile	Leu	Thr	His	Leu	Lys	Val	Ser
		595					600					605			
Phe	Ser	Arg	Asp	Ala	Pro	Val	Gly	Glu	Glu	Glu	Ala	Pro	Ala	Lys	Tyr
	610					615					620				
Val	Gln	Asp	Asn	Ile	Gln	Leu	His	Gly	Gln	Gln	Val	Ala	Arg	Ile	Leu
625					630					635					640
Leu	Gln	Glu	Asn	Gly	His	Ile	Tyr	Val	Cys	Gly	Asp	Ala	Lys	Asn	Met
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Gly	Val	Glu	Lys	Leu	Glu	Ala	Met	Lys	Thr	Leu	Ala	Thr	Leu	Lys	Glu
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 <212> DNA  
 <213> Homo sapiens

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 <212> PRT  
 <213> Homo sapiens

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Ala Asp Leu His Cys Ile Ser Glu Ser Asp Lys Tyr Asp Leu Lys Thr
 35          40          45
Glu Thr Ala Pro Leu Val Val Val Ser Thr Thr Gly Thr Gly Asp
 50          55          60
Pro Pro Asp Thr Ala Arg Lys Phe Val Lys Glu Ile Gln Asn Gln Thr
 65          70          75          80
Leu Pro Val Asp Phe Phe Ala His Leu Arg Tyr Gly Leu Leu Gly Leu
 85          90          95
Gly Asp Ser Glu Tyr Thr Tyr Phe Cys Asn Gly Gly Lys Ile Ile Asp
100         105         110
Lys Arg Leu Gln Glu Leu Gly Ala Arg His Phe Tyr Asp Thr Gly His
115         120         125
Ala Asp Asp Cys Val Gly Leu Glu Leu Val Val Glu Pro Trp Ile Ala
130         135         140
Gly Leu Trp Pro Ala Leu Arg Lys His Phe Arg Ser Ser Arg Gly Gln
145         150         155         160
Glu Glu Ile Ser Gly Ala Leu Pro Val Ala Ser Pro Ala Ser Leu Arg
165         170         175
Thr Asp Leu Val Lys Ser Glu Leu Leu His Ile Glu Ser Gln Val Glu
180         185         190
Leu Leu Arg Phe Asp Asp Ser Gly Arg Lys Asp Ser Glu Val Leu Lys
195         200         205
Gln Asn Ala Val Asn Ser Asn Gln Ser Asn Val Val Ile Glu Asp Phe

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Asn Ile Pro Gly Leu Pro	Pro Glu Tyr Leu Gln Val His Leu Gln Glu			
245	250	255		
Ser Leu Gly Gln Glu Glu	Ser Gln Val Ser Val Thr Ser Ala Asp Pro			
260	265	270		
Val Phe Gln Val Pro Ile	Ser Lys Ala Val Gln Leu Thr Thr Asn Asp			
275	280	285		
Ala Ile Lys Thr Thr Leu	Leu Val Glu Leu Asp Ile Ser Asn Thr Asp			
290	295	300		
Phe Ser Tyr Gln Pro Gly	Asp Ala Phe Ser Val Ile Cys Pro Asn Ser			
305	310	315	320	
Asp Ser Glu Val Gln Ser	Leu Leu Gln Arg Leu Gln Leu Glu Asp Lys			
325	330	335		
Arg Glu His Cys Val Leu	Leu Lys Ile Lys Ala Asp Thr Lys Lys Lys			
340	345	350		
Gly Ala Thr Leu Pro Gln	His Ile Pro Ala Gly Cys Ser Leu Gln Phe			
355	360	365		
Ile Phe Thr Trp Cys Leu	Glu Ile Arg Ala Ile Pro Lys Lys Ala Phe			
370	375	380		
Leu Arg Ala Leu Val Asp	Tyr Thr Ser Asp Ser Ala Glu Lys Arg Arg			
385	390	395	400	
Leu Gln Glu Leu Cys Ser	Lys Gln Gly Ala Ala Asp Tyr Ser Arg Phe			
405	410	415		
Val Arg Asp Ala Cys Ala	Cys Leu Leu Asp Leu Leu Leu Ala Phe Pro			
420	425	430		
Ser Cys Gln Pro Pro Leu	Ser Leu Leu Leu Glu His Leu Pro Lys Leu			
435	440	445		
Gln Pro Arg Pro Tyr Ser	Cys Ala Ser Ser Ser Leu Phe His Pro Gly			
450	455	460		
Lys Leu His Phe Val Phe	Asn Ile Val Glu Phe Leu Ser Thr Ala Thr			
465	470	475	480	
Thr Glu Val Leu Arg Lys	Gly Val Cys Thr Gly Trp Leu Ala Leu Leu			
485	490	495		
Val Ala Ser Val Leu Gln	Pro Asn Ile His Ala Ser His Glu Asp Ser			
500	505	510		
Gly Lys Ala Leu Ala Pro	Lys Ile Ser Ile Ser Pro Arg Thr Thr Asn			
515	520	525		
Ser Phe His Leu Pro Asp	Asp Pro Ser Ile Pro Ile Ile Met Val Gly			
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Pro Gly Thr Gly Ile Ala	Pro Phe Ile Gly Phe Leu Gln His Arg Glu			
545	550	555	560	
Lys Leu Gln Glu Gln His	Pro Asp Gly Asn Phe Gly Ala Met Trp Phe			
565	570	575		
Phe Gly Cys Arg His Lys	Asp Arg Asp Tyr Leu Phe Arg Lys Glu Leu			
580	585	590		
Arg His Phe Leu Lys His	Gly Ile Leu Thr His Leu Lys Val Ser Phe			
595	600	605		
Ser Arg Asp Ala Pro Val	Gly Glu Glu Glu Ala Pro Ala Lys Tyr Val			
610	615	620		



Gln Asp Asn Ile Gln Leu His Gly Gln Gln Val Ala Arg Ile Leu Leu  
 625 630 635 640  
 Gln Glu Asn Gly His Ile Tyr Val Cys Gly Asp Ala Lys Asn Met Ala  
 645 650 655  
 Lys Asp Val His Asp Ala Leu Val Gln Ile Ile Ser Lys Glu Val Gly  
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 <212> DNA  
 <213> Homo sapiens

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2093

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 Thr Ala Pro Leu Val Val Val Val Ser Thr Thr Gly Thr Gly Asp Pro  
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 Pro Val Asp Phe Phe Ala His Leu Arg Tyr Gly Leu Leu Gly Leu Gly  
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 Asp Ser Glu Tyr Thr Tyr Phe Cys Asn Gly Gly Lys Ile Ile Asp Lys  
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 Arg Leu Gln Glu Leu Gly Ala Arg His Phe Tyr Asp Thr Gly His Ala  
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 Asp Asp Cys Val Gly Leu Glu Leu Val Val Glu Pro Trp Ile Ala Gly  
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 Leu Arg Phe Asp Asp Ser Gly Arg Lys Asp Ser Glu Val Leu Lys Gln  
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 Asn Ala Val Asn Ser Asn Gln Ser Asn Val Val Ile Glu Asp Phe Glu  
 210 215 220  
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 225 230 235 240  
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 Leu Gly Gln Glu Glu Ser Gln Val Ser Val Thr Ser Ala Asp Pro Val  
 260 265 270  
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 275 280 285  
 Ile Lys Thr Thr Leu Leu Val Glu Leu Asp Ile Ser Asn Thr Asp Phe  
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